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April 15, 2003

PATENT APPLICATION
Attorney's Docket No.: 1314.1058-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Timothy P. Tully, Joshua I. Dubnau, Michael Davis, Jan Mous
and Ulrich Certa

Application No.: 09/523,066 Group Art Unit: 1634

Filed: March 10, 2000 Examiner: B. Forman

Confirmation No.: 4462

For: GENE CHIP TECHNOLOGY FOR DETERMINING MEMORY GENES

CERTIFICATE OF MAILING	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202	
on 4-15-03	<i>Dawn Myers</i>
Date	Signature
<i>Dawn Myers</i>	
Typed or printed name of person signing certificate	

DECLARATION OF TIMOTHY P. TULLY, PH.D.UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Sir:

I, Timothy P. Tully, Ph.D., of 28 Fairway Place, Cold Spring Harbor, New York 11724, declare and state that:

1. I am one of the inventors of the subject matter described and claimed in U.S. Provisional Application No. 60/124,085 ('085), filed March 10, 1999 and U.S. Application No. 09/523,066 ('066), filed March 10, 2000. The '066 application claims the benefit of the '085 application.

EXHIBIT

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2. I have read the Office Action dated April 10, 2002 (Paper No. 14) and the cited references of Yin *et al.* (*Cell*, 79:49-58 (1994)), Ramsey (*Nature Biotechnology*, 16:40-44 (1998)) and Tully *et al.* (U.S. Patent No. 5,929,223). I have also read the claims that were rejected in the Office Action.

3. Yin *et al.* teach the use of a dominant negative CREB transgene to investigate the role of CREB in long term memory (LTM) formation in *Drosophila*. In particular, Yin *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB transgene on LTM formation. More specifically, Yin *et al.* teach the production of transgenic flies that express *dCREB2-b* under the control of a heat-shock promoter (*hs-dCREB2-b* transgene), training the transgenic flies which had been heat-shock induced or left uninduced, under conditions appropriate to induce memory formation in the flies, extracting RNA from the head tissue of trained flies, exposing the extracted RNA to a *dCREB2-b* cDNA fragment under conditions appropriate for hybridization of *dCREB2-b* transgene RNA to the *dCREB2-b* cDNA fragment and detecting hybridization of *dCREB2-b* transgene RNA to the *dCREB2-b* cDNA fragment. The hybridization signal detected using RNA extracted from the heads of trained transgenic flies is compared to the hybridization signal detected using RNA extracted from the heads of wildtype flies (i.e., flies that do not include the *hs-dCREB2-b* transgene) trained in the same manner as the transgenic flies (Yin *et al.*, page 50, Figure 1A).

Yin *et al.* also disclose the results of behavioral experiments in which the performance index of the trained flies is measured (Yin *et al.*, page 51, column 2 to page 53, column 2) and provide methods for statistically analyzing the behavioral data obtained (Yin *et al.*, page 55, column 2, second paragraph from bottom ("Statistical Analyses of Behavioral Data") to page 56, column 2, fourth full paragraph ("Shock Reactivity in *rsh;17-2* Flies (Table 1)").

4. Example 2 of the Tully *et al.* patent is the same as or similar to the "Experimental Procedures" (pages 55 to 57) and "Results" (pages 50 to 53) sections of the Yin *et al.* reference.

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At column 25, lines 6-30, Tully *et al.* disclose the method for performing Northern analysis, which is the same as or similar to the method disclosed by Yin *et al.* (see Yin *et al.*, at page 56, column 2, last paragraph). At column 26, lines 9-15, Tully *et al.* report the results revealed by Northern analysis, which are the same as or similar to the results reported by Yin *et al.* (see Yin *et al.*, at page 50, column 2, last paragraph).

Similarly, in Example 2, Tully *et al.* teach the use of a dominant negative CREB transgene to investigate the role of CREB in LTM formation in *Drosophila*. In particular, Tully *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB transgene on LTM formation. More specifically, Tully *et al.* teach the production of transgenic flies that express *dCREB2-b* under the control of a heat-shock promoter (*hs-dCREB2-b* transgene), training the transgenic flies which had been heat-shock induced or left uninduced, under conditions appropriate to induce memory formation in the flies, extracting RNA from the head tissue of trained flies, exposing the extracted RNA to a *dCREB2-b* cDNA fragment under conditions appropriate for hybridization of *dCREB2-b* transgene RNA to the *dCREB2-b* cDNA fragment and detecting hybridization of *dCREB2-b* transgene RNA to the *dCREB2-b* cDNA fragment. The hybridization signal detected using RNA extracted from the heads of trained transgenic flies is compared to the hybridization signal detected using RNA extracted from the heads of wildtype flies (i.e., flies that do not include the *hs-dCREB2-b* transgene) trained in the same manner as the transgenic flies (Tully *et al.*, column 3, lines 36-41; and Figure 9A).

In Example 2, Tully *et al.* also disclose the results of behavioral experiments in which the performance index of the trained flies is measured (Tully *et al.*, column 26, line 52 to column 28, line 41) and provide methods for statistically analyzing the behavioral data obtained (Tully *et al.*, column 23, line 1 to column 25, line 5).

5. Neither Yin *et al.* nor Tully *et al.* suggest that their results can be achieved using microarray chip analysis. Yin *et al.* and Tully *et al.* simply demonstrate that functional regulation of CREB itself is both necessary and sufficient for modulation of long-term memory formation (LTM). Downregulation of CREB leads to suppression of LTM. Upregulation of CREB leads to

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enhancement of LTM. Tully *et al.* also disclose drug or gene manipulations to accomplish this modulation of CREB and the corresponding enhancement/suppression of long-term memory formation. While both these references may suggest "downstream" genes conceptually, neither mentions it explicitly and neither provides any explicit methods (e.g., DNA microarray techniques) to identify such genes.

6. Ramsey describes the state of the art of DNA chip technology, including its successful application "to the simultaneous expression of many thousands of genes and to large-scale gene discovery" (Ramsey, page 40, abstract). For example, Ramsey reports the successful use of DNA arrays to measure differential gene expression in plants, yeast and human samples (Ramsey, page 41, column 1). Thus, Ramsey describes only a general method to detect transcriptionally regulated genes using DNA microarray techniques. Importantly, Ramsey does not describe in detail any specific statistical method for the selection of significant treatment effects from such microarray data, and he does not describe any specific method to identify any specific subset of genes, which are transcriptionally regulated during long-term memory formation. Yin *et al.* and Tully *et al.* provided the data to suggest that particular comparisons of behavioral training protocols might be used conceptually to detect transcriptionally regulated genes specific to the long-term memory formation experimentally induced (odor-shock associations) as distinct from those transcriptionally regulated genes that might respond to other nonspecific stimuli in the animals' environment/life history.

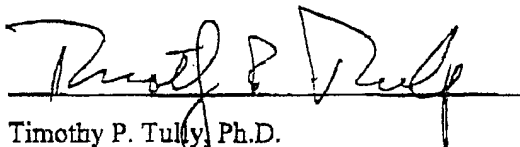
In contrast, the subject application teaches a specific set of microarray comparisons that can be used to identify downstream genes, which are specifically regulated during long-term memory formation, and upon which an appropriate statistical method may be performed. This combination of methods (comparison of particular behavioral training protocols and statistical method) is not disclosed by the cited combination of references.

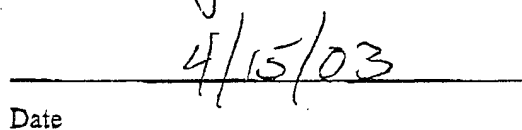
7. I declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements and the like made

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by me are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.


Timothy P. Tully, Ph.D.


Date